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09/121,239	07/23/1998	RICHARD C. HARVEY	GP091-02.UT	3098

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GEN PROBE INCORPORATED
10210 GENETIC CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	25

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/121,239	Applicant(s) HARVEY ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 24 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-20 are pending upon entry of the amendment filed 11/13/01. The claims are newly rejected under 35 U.S.C. 102, 35 U.S.C. 103 and 35 U.S.C. 112 as follows:

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 4 and 6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 6 are indefinite for the language "stable hybridization complex" since the metes and bounds of a "stable" complex are unclear. Any interaction at all would be considered better than no interaction, so the extent of binding which renders the complex "stable" is not clearly defined.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-5 and 9-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Sooknanan et al. (Experimental Hematology 21:1719-1724, 1993).

Sooknanan et al. teach the methods of claims 1 and 9 to detect a fusion nucleic acid (such as BCR-ABL, see title) by (a) providing a sample containing a first single-stranded fusion nucleic acid comprising a splice junction (such as the Bcr-Abl fusion RNA from Ph+ CML blood cells, page 1719, col. a, line 40-44, and col. b, lines 8-30), (b) contacting under nucleic acid amplification conditions the first single-stranded fusion nucleic acid, a first primer which hybridizes to the fusion nucleic acid at a first primer binding site located 3' to the splice junction site (page 1719, col. b, lines 32-44, especially lines 39-41 for the primer), and at least one nucleic acid polymerase activity (page 1719, col. a, lines 42-45), and (c) amplifying the fusion nucleic acid in an isothermal (page 1719, col. A, lines 42-44) nucleic acid amplification reaction using the first primer to produce a plurality of second nucleic acid strands complementary to at least a portion of the first single-stranded fusion nucleic acid that contains the splice junction site (page 1719, col. b, last para., through page 1720, col. a, first para.), and a second probe binding site located 5' to and not overlapping the complementary splice junction site, wherein the second probe binding site overlaps or is located 3' to sequence complementary to the first primer binding site (see use of the T7 promoter primer in the NASBA reaction, page 1720, col. a, first para. and Figure 1, page 1721; furthermore, there are inherently probe binding sites on either side of the junction site and

that the probes come from different chromosomes as claimed in claims 11 and 12, since it is inherent that such translocation junctions provide a sequence on either side of the junction originating from two chromosomes or from within the same chromosome), (d) hybridizing the second nucleic acid strands with an oligonucleotide probe under hybridization conditions in which the probe hybridizes to either the first probe binding site or the second probe binding site, thereby forming a probe:target hybrid (again, see Figure 1, page 1721 for use of two primers in the NASBA reaction and description of analysis of amplified products on page 1720 which teaches use of two probes), and (e) detecting the probe:target hybrid as an indication of the presence of the fusion nucleic acid in the sample (page 1720, col. b, lines 19-20, detection by autoradiography).

Sooknanan et al. further anticipates claims 2-5, 10 and 16-17 by teaching the following limitations: the first single-stranded fusion nucleic acid is an mRNA (see page 1720, col. b, the first single-stranded fusion nucleic acid is mRNA from Ph+CML cells), the first primer is a promoter-primer (see Figure 1, page 1721, which shows amplification of the mRNA using T7 promoter primer), the polymerase activity comprises an RNA polymerase activity (see Figure 1, page 1721 for use of T7 RNA Polymerase), the oligonucleotide probe is of the same sense as the mRNA and binds to the first probe binding site (see page 1720, col. b for a description of the probes, since the probes are detecting DNA, it is inherent that they would have the same sequence as the mRNA), wherein the second nucleic acid strands are complementary RNA (see Figure 1, page 1721 for production of the complementary RNA), wherein the amplifying step includes

contacting the second nucleic acid strand with a second primer or promoter-primer which hybridizes to a second primer binding site located 3' to both the complementary splice junction and the first probe binding site (see Figure 1, page 1721, for the use of additional promoter-primers in the NASBA reaction), wherein the amplifying step uses a DNA-directed DNA polymerase activity and an RNA-directed DNA polymerase activity (both functions are carried out by RT, see Figure 1, page 1721 for use of RT in the NASBA reaction). Claims 13-15 are anticipated by Sooknanan et al. since they teach amplification of the Bcr-Abl translocation (also known as t(9;22)) using methods encompassing use of the T7 primer (instant SEQ ID NO:1).

6. Claims 19 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Qiagen Oligotex Direct Protocol for isolation of PolyA+ mRNA from cytoplasm of cultured cells (reference in Qiagen product guide, 1/98, page 61 and protocol from Qiagen web page www.qiagen.com).

Qiagen teaches a method for preparing a sample containing RNA suitable for amplification (they teach purification of RNA from cultured cells), via the steps of (a) providing a biological sample comprising unpurified RNA (they teach starting with cells from cell culture), mixing the biological sample with a solution consisting essentially of a buffer at a pH of about 6.5 to about 8.5, about 150mM to about 1M of a soluble salt, and about 0.5% to about 1.5% (v/v) of a non-ionic detergent, to produce a solution containing released RNA (they teach use of the OCL buffer having a pH of 7.5, 145mM of NaCl + KCl soluble salts, and 1% of the non-ionic detergent

Nonidet P-40, see Appendix C for the concentrations of the OCL buffer), mixing the solution containing released RNA with a solid support to which is joined an immobilized oligonucleotide comprising a nucleotide base sequence which forms a stable immobilized oligonucleotide: RNA hybridization complex under hybridization conditions (they teach on page 45, step 5, hybridization of the RNA with an oligo dT30 linked to the Oligotex particles and the poly-A tail of the mRNA), separating the hybridization complex joined to the solid support from unhybridized sample components (they teach pelleting the oligotex:mRNa complex by centrifugation and removal of the supernatant containing the unhybridized sample components), and washing the hybridization complex joined to the solid support with a solution having sufficient salt concentration to maintain the hybridization complex, thereby not requiring extraction using reagents such as phenol or chloroform to prepare RNA (they teach resuspension of the oligotex:mRNA pellet in the buffer OL1, OW1 and OW2 for final suspension of the RNA product). The methods taught by Qiagen may be applied to whole cells, including those from blood, plasma or bone marrow for instance.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sooknanan et al. in view of Qiagen Oligotex Direct protocol for isolation of Poly A+ mRNA as set forth above.

Sooknanan et al teaches the limitations of claims 1-5 and 9-17 as discussed above.

Qiagen teaches the limitations of claims 19 and 20 as discussed above.

Qiagen teaches a method for preparing a sample containing RNA suitable for amplification (they teach purification of RNA from cultured cells), via the steps of (a) providing a biological sample comprising unpurified RNA (they teach starting with cells from cell culture), mixing the biological sample with a solution consisting essentially of a buffer at a pH of about 6.5 to about 8.5, about 150mM to about 1M of a soluble salt, and about 0.5% to about 1.5% (v/v) of a non-ionic detergent, to produce a solution containing released RNA (they teach use of the OCL buffer having a pH of 7.5, 145mM of NaCl + KCl soluble salts, and 1% of the non-ionic detergent Nonidet P-40, see Appendix C for the concentrations of the OCL buffer), mixing the solution containing released RNA with a solid support to which is joined an immobilized oligonucleotide

comprising a nucleotide base sequence which forms a stable immobilized oligonucleotide: RNA hybridization complex under hybridization conditions (they teach on page 45, step 5, hybridization of the RNA with an oligo dT30 linked to the Oligotex particles and the poly-A tail of the mRNA), separating the hybridization complex joined to the solid support from unhybridized sample components (they teach pelleting the oligotex:mRNa complex by centrifugation and removal of the supernatant containing the unhybridized sample components), and washing the hybridization complex joined to the solid support with a solution having sufficient salt concentration to maintain the hybridization complex, thereby not requiring extraction using reagents such as phenol or chloroform to prepare RNA (they teach resuspension of the oligotex:mRNA pellet in the buffer OL1, OW1 and OW2 for final suspension of the RNA product). The methods taught by Qiagen may be applied to whole cells, including those from blood, plasma or bone marrow for instance.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to practice the methods taught by Sooknanan et al. with the RNA purification methods taught by Qiagen since Qiagen taught methods of RNA isolation from whole cells useful for many purposes including amplification reactions such as the NASBA reactions taught by Sooknanan et al.

One of ordinary skill in the art would have been motivated to substitute the RNA isolation method taught by Qiagen for the RNA isolation methods taught by Sooknanan et al. (Page 1719, col. b) since Qiagen et al. taught use of their methods for isolation of RNA from whole cells, such as the whole cells taught by Sooknanan et al. One of ordinary skill in the art would have had an

expectation of success to practice the RNA isolation methods of Sooknanan et al. with the Qiagen RNA isolation methods since Qiagen taught isolation of RNA from whole cells such as those used by Sookanan et al.

Applicant should note that for the particular buffer reagents, it would further have been *prima facie* obvious to perform routine optimization using reagents, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific buffer concentrations were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Applicant should note regarding any unexpected results which might be argued to overcome the issue of routine optimization that MPEP 716.01(c) makes clear "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

9. Claims 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sooknanan et al. in view of Qiagen Oligotex Direct protocol for isolation of Poly A+ mRNA as set forth above and further in view of Burg et al. (U.S. Patent 6,300,068 B1).

Sooknanan in view of Qiagen teach the limitations of claims 1-17, 19 and 20 as discussed above.

Claim 18 further limits the method of claim 9 by adding the limitation wherein the amplifying step also amplifies an internal control transcript in the sample by using the first primer and then hybridizing a second oligonucleotide probe which hybridizes to the complement of the internal control transcript but does not hybridize to the complement of the fusion mRNA transcript thereby forming an internal control hybridization complex, and wherein the detecting step also detects the presence of the internal control hybridization complex in the sample, thereby providing an internal standard. As taught above, Sooknanan et al. taught the methods of claim 9, but did not teach methods having an internal control transcript.

Burg et al. teaches the use of an internal control transcript in methods of nucleic acid amplification. Specifically Burg taught "The construction of internal control sequences composed of functional building blocks of sequences chosen by random generation of nucleic acid sequence for use as amplification reaction internal positive controls ideally requires that the control sequences be specifically designed to be used for the various nucleic acid amplification protocols including but not limited to PCR, LCR, TMA, NASBA, and SDA. The internal control nucleic acid sequence, in combination with the appropriate sequence specific oligonucleotide primers or

promoter-primers will generate a positive amplification signal if the amplification reaction was successfully completed." (From col. 22, example 6)

It would have been further obvious to use internal control sequences (as taught by Burg et al.) in the NASBA methods taught by Sooknanan et al. since Burg et al. explicitly contemplates use of internal control sequences in NASBA methods (col. 22, Example 6, line 17). One of ordinary skill in the art would have been motivated to use the internal control sequences taught by Burg et al. in the methods taught by Sooknanan et al. in view of Qiagen since the methods taught by Sooknanan et al. were NASBA reactions and Burg et al. directly suggested the use of internal control sequences in NASBA reactions. One of ordinary skill in the art would have had an expectation of success to use internal control sequences in the NASBA methods taught by Sookanan et al. since Burg et al. taught the use of internal control sequences in NASBA reactions.

Response to Arguments

10. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

JEFFREY FREDMAN
PRIMARY EXAMINER

M. M. Schmidt
December 21, 2001